Lipoid Proteinosis (Urbach-Wiethe Disease): A Rare Genodermatosis with Characteristic Dermatological and Neuroimaging Findings

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Case Study

A 38-year-old male of South Asian ancestry born of third-degree consanguineous marriage was first noted to have progressive hoarseness of voice at one year of age. Subsequently, he developed beaded papules along the eyelids, papulonodular waxy lesions along the forehead, verrucous lesions along the extensor aspects of the fingers, with early-onset alopecia. At the age of 23 years, he started experiencing nocturnal bilateral tonic-clonic seizures. His seizures were uncontrolled on sodium valproate (1000 mg/day) at the time of his first consultation.

On examination, characteristic eyelid and skin lesions were noted, leading us to consider a diagnosis of lipoid proteinosis [Figure 1]. Electroencephalogram showed bilateral frontotemporal high amplitude slowing [Figure 2a].

Computed tomography (CT) of the brain showed bilateral dense curvilinear calcifications in the amygdalae and the head of the hippocampi [Figure 2b]. He was started on oxcarbazepine (900 mg/day), and has been seizure-free for a year.

Genetic testing done for confirmation of the diagnosis revealed homozygous mutation in Extra-Cellular Matrix protein 1 (ECM1) gene on chromosome 1q21 (c.966del p.Glu323SerfsTer20). This leads to a homozygous base pair deletion in exon 7 of the ECM1 gene and results in a frameshift and premature truncation of the protein 20 amino acids downstream to codon 323.

Discussion

Lipoid proteinosis (LP) was first described by Urbach and Wiethe in 1929 as "hyalinosis cutis et mucosae." It is a rare, autosomal-recessive genodermatosis caused by a mutation in the ECM1 gene on chromosome 1q21 and has varied dermatological and neuropsychiatric symptoms depending on the pattern of deposition of the abnormal glycoprotein.[1] Mutations lead to deposition of amorphous hyaline material that is periodic acid Schiff (PAS) positive in the dermis, with thickening of the skin and mucous basement membranes, blood vessels, and adnexal epithelia.[2] This produces excessive scarring and poor wound healing, with premature aging of the skin.[2] Hoarseness is present in early childhood in approximately two-thirds due to infiltration of the larynx.

Nervous system involvement is seen in 50 to 75%, and may present as migraine, epilepsy, depression, anxiety disorder, or cognitive dysfunction.[1] Infiltration of the hippocampal capillaries, resulting in thickened walls of the blood vessels, and perivascular calcium deposition is the underlying mechanism. Tieve *et al*.[3] described a patient who presented with the characteristic cutaneous findings, and childhood-onset generalized dystonia with bilateral symmetrical striatal calcifications. Spontaneous intracerebral hemorrhage affecting the basal ganglia without any other risk factors has also been described.[4]

The typical finding in LP is dense calcification that selectively and symmetrically affects the medial temporal lobes.[5,6]

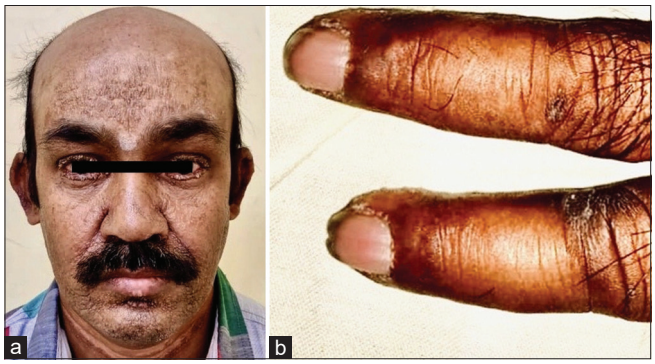

Figure 1: Dermatological findings. (a) Papulonodular waxy lesions over the forehead and chin, with characteristic beaded papules along the eyelids (monoliform blepharosis), and alopecia. (b) Verrucous lesions on the extensor aspect of the interphalangeal joints of the fingers

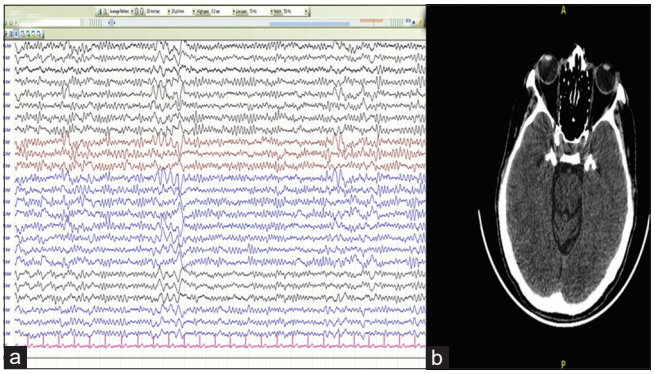

Figure 2: Investigation findings. (a) Electroencephalogram showing frontotemporal slowing in average referential montage. (b) Axial CT brain shows comma-shaped amydalo-hippocampal calcification due to abnormal hyaline deposition in the capillaries

Amygdala involvement is pathognomonic and becomes more prominent with longer durations of the disease. The commonest involved sites are the amygdalae, hippocampi, parahippocampal gyri, and striatum. The calcifications appear as curvilinear or comma-shaped hyperdense lesions located symmetrically in both medial temporal lobes and the corpus striatum on CT. These lesions are hypointense on T1- and T2-weighted images on magnetic resonance imaging (MRI) and are best seen on gradient echo (GRE) or susceptibility weighted imaging (SWI) sequences.

The predilection for the involvement of the medial temporal lobes and amygdalae probably explain the neurological manifestations of memory deficits, epilepsy, and mood disorders. Differential diagnosis for medial temporal lobe calcifications include calcified gliomas in the amygdalohippocampal region in pediatric patients, but these are neither bilateral nor symmetrical; Raine syndrome, which is a rare autosomal recessive osteosclerotic bone dysplasia, characterized by intracranial calcifications in the basal ganglia which do not involve the amygdalae, and healed herpes encephalitis lesions.

Typically, LP is slowly progressive and does not shorten life expectancies. Management involves symptomatic relief and treatment of complications. Epilepsy, migraine, dystonia, and stroke secondary to LP are treated along general guidelines.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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